REMARKS

Claims 1-11 and 20-26 are pending.

Claims 1-8 and 20-26 are rejected. Claims 1 and 2 have been amended. Support for the amendments can be found throughout the specification and claims as originally filed. For instance, support may be found at page 7, line 26 – page 8, line 14. No new matter has been added.

In view of the following remarks, the Examiner is requested to allow Claims 1-8 and 20-26, the only claims pending and under examination in this application.

Allowable subject matter

The Applicants thank the Examiner for indicating that claims 9-11 recite allowable subject matter.

Abstract

The abstract has been objected to because it exceeds the maximum allowable length.

The abstract has been amended in accordance with the Examiner's suggestion.

It is believed that this objection has been addressed. Acknowledgement of such is requested.

Claim Rejections - 35 U.S.C. § 112, first paragraph

Claims 2-5 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite.

In support of this rejection, the Office asserts that it is unclear whether the phrase "representing a set of genes" in line 3 of claim 2 refers to the same set of genes previously recited or to a different set of genes.

Without any intention to acquiesce to the correctness of this rejection and solely to expedite prosecution, claim 2 has been amended as indicated above to make it explicitly clear that the set of genes referred to in line 3 of claim 2 is the

same set of genes previously recited. As claims 3-5 each depend from claim 2, this amendment adequately addresses the rejection as applied to those claims.

Applicants submit that the rejection of claims 2-5 under 35 U.S.C. § 112, second paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Claim Rejections - 35 U.S.C. § 102(b)

Claims 1-4 and 6-8 were rejected under 35 U.S.C. 102(b) as allegedly anticipated by Bonaventure et al. (Brain Research, Vol. 943, Pages 38-47, July 2002) ("Bonaventure"). The Applicants respectfully traverse this rejection.

It is well established that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

As best understood by the Applicants, the claims are rejected as anticipated because the phrase "for evaluating the ability of an oligonucleotide probe to measure differential expression of genes" as found in the preamble of claim 1 is interpreted as an intended use which does not differentiate the method over the prior art.

The Applicants disagree with the Examiner's line of reasoning and conclusion. Nevertheless, without any intention to acquiesce to the correctness of this rejection and solely to expedite prosecution, claim 1 has been amended to recite "(c) selecting said combination of nucleic acid sample pairs as the combination of nucleic acid sample pairs for evaluating the ability of an oligonucleotide probe to measure differential expression of genes". As such, it is clear that the combination of nucleic acid sample pairs described in (b) is selected, as part of the claimed method, as the combination of nucleic acid sample pairs for evaluating the ability of an oligonucleotide probe to measure differential expression of genes.

Bonaventure fails to disclose element (c) of the rejected claims and, as such, fails to anticipate the rejected claims.

Bonaventure discusses nuclei and subnuclei gene expression profiling in mammalian brain. Gene expression profiles were measured from seven different laser-captured brain nuclei or subnuclei in three adult rats (Fig. 2a). Genes were considered expressed if the difference to the background was significant. The author

presented data on the number of genes that were enriched in one nucleus with respect to the six other nuclei (see Table 1). Pair-wise scatter plots were used to determine correlation between different nuclei. Bonaventure indicates that their hierarchical cluster analysis demonstrated that each of the seven nuclei had a unique gene expression profile and that there was a molecular basis for the previously defined anatomic nuclei or subnuclei (see column 2, page 46).

As indicated above, Bonaventure is concerned with gene expression profiling. The authors evaluated expression among brains of different subjects for the purpose of understanding aspects of brain biology. There is no discussion in Bonaventure of selecting a combination of nucleic acid sample pairs for evaluating the ability of an oligonucleotide probe to measure differential expression of genes. Since claim 1 as currently amended requires "selecting said combination of nucleic acid sample pairs as the combination of nucleic acid sample pairs for evaluating the ability of an oligonucleotide probe to measure differential expression of genes," Bonaventure therefore fails to disclose each and every element of claim 1. As such, Bonaventure cannot anticipate claim 1.

Claims 2-4 and 6-8 are patentable over Bonaventure at least as a result of their respective dependencies from claim 1, which, as demonstrated above, is patentable over the teaching of Bonaventure.

Applicants submit that the rejection of claims 1-4 and 6-8 under 35 U.S.C. § 102(b) has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Claim Rejections - 35 U.S.C. § 102(e)

Claims 1-8 and 20-26 were rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Collins et al. (U.S. Publication No. 2004/0101846, filed November 22, 2002) ("Collins"). The Applicants respectfully traverse this rejection.

Collins fails to disclose or suggest at least the following elements of amended claim 1: (i) identifying a combination of nucleic acid sample pairs in relation to the members of said combination having a maximized number of genes from the set of genes that exhibit differential expression and a minimized number of genes from the set of genes that do not exhibit differential expression; and (ii) selecting said combination of nucleic acid sample pairs as the combination of nucleic acid sample

pairs for evaluating the ability of an oligonucleotide probe to measure differential expression of genes. As such, this rejection should be withdrawn.

The Office asserts that Collins discloses selection of nucleic acid sample pairs by hybridizing nucleic acid sample pairs to nucleic acids on microarrays and selecting for those sample pairs that maximize the number of mRNAs that are differentially expressed. The Office further asserts that since Collins is detecting differential expression, the different pairs must comprise different nucleic acid samples.

The passage from the reference relied on by the Office (paragraph 70, lines 1-8), however, discusses a representative example of the empirical evaluation step of the methods disclosed in the reference. Multiple copies of a microarray that includes candidate 60-mer probes having sequences identified by the prior sequence identification step were produced using an *in situ* nucleic acid array synthesis protocol. These resultant microarrays were than hybridized to 10 different tissue/cell line combinations (4 replicates per sample pair): one self-vs.-self and 9 sample pairs chosen to maximize the number of mRNAs that are differentially expressed between the members of the pair.

It is clear from the context in which the above passage is presented (see paragraphs 0048, *et seq.*) that Collins discusses a method for identifying candidate probes for a target nucleic acid and not a method for selecting a combination of nucleic acid sample pairs for evaluating the ability of an oligonucleotide probe to measure differential expression of genes, as required by the instant claims. For example, at paragraph 48, Collins indicates that the invention provides methods of identifying a sequence of a nucleic acid that is suitable for use as a surface immobilized probe for a target nucleic acid.

Thus, claim 1 recites a method that is different to that described by Collins.

Claims 2-8 are patentable over Collins at least as a result of their respective dependencies from claim 1, which, as demonstrated above, is patentable over the teaching of Collins.

With respect to claim 20, the Office alleges that Collins discloses evaluating candidate probes using sample pairs identified through the method of claim 1 (referring to paragraph 69).

As demonstrated above, Collins does not disclose or suggest the method of

amended claim 1, i.e., a method for selecting a combination of nucleic acid sample pairs for evaluating the ability of an oligonucleotide probe to measure differential expression of genes which requires "selecting said combination of nucleic acid sample pairs as the combination of nucleic acid sample pairs for evaluating the ability of an oligonucleotide probe to measure differential expression of genes." Therefore, claim 20 is patentable over Collins at least by virtue of its dependency from claim 1.

Claims 21-26 are patentable over Collins for the reasons discussed above with respect to the patentability of claims 1 and 20 over Collins.

Applicants submit that the rejection of claims 1-8 and 20-26 under 35 U.S.C. § 102(e) has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Claim Rejections - 35 U.S.C. § 103(a)

Claims 20-24 and 26 were rejected under 35 U.S.C. § 103(a) as allegedly obvious over Dooley et al. (U.S. Patent Publication No. 2001/0046671, Publication Date Nov. 29, 2001) ("Dooley") in view of Bonaventure et al. (Brain Research, Vol. 943, pages 38-47, July, 2002) ("Bonaventure").

The Patent Office bears the burden of establishing a *prima facie* case of obviousness under 35 U.S.C. § 103. *In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988); *In re Duel*, 51 F.3d 1557 (Fed. Cir. 1995). To establish a prima facie case of obviousness the prior art reference, or references when combined, must teach or suggest all the claim limitations. In re Royka, 180 USPQ 580 (CCPA 1974). In addition, one should guard against a "temptation to read into the prior art the teachings of the invention in issue" and "guard against slipping into the use of hindsight." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1742 (U.S. 2007), (quoting *Graham v. John Deere Co.*, 383 U.S., at 36, 86 S. Ct. 684, 15 L. Ed. 2d 545).

As stated by the Office, Dooley does not disclose using a sample pair from claim 1. The Office alleges, however, that Bonaventure discloses obtaining a sample pair by a method of claim I. The Office asserts that it would have been obvious for one of ordinary skill in the art, at the time the invention was made, to modify the method of Bonaventure to use it in combination with the method of Dooley to prepare probes that are specific for the tissue pair of Bonaventure. According to the Office,

one of ordinary skill in the art would have been motivated to do this because, as suggested by Dooley, by designing an "informative array," Bonaventure would be more likely to identify differentially expressed genes (referring to paragraph 19, lines 4-8).

Without acquiescing in the assertions of the Office regarding the disclosure of Dooley, Bonaventure, as demonstrated above, does not disclose or suggest a method as claimed in amended claim 1. Therefore, even if the combination of teachings of the references were made as asserted by the Office, one still would not be in possession of the presently claimed methods of claims 20-24 and 26. Dooley does not cure the deficiencies of Bonaventure. The combined teachings of Bonaventure and Dooley do not disclose or suggest at least the following element of amended claim 1: (c) selecting said combination of nucleic acid sample pairs as the combination of nucleic acid sample pairs for evaluating the ability of an oligonucleotide probe to measure differential expression of genes.

Bonaventure and Dooley, either individually or in combination, do not disclose or suggest the method of claim 1. Accordingly, substituting the teaching of Bonaventure in that of Dooley does not result in the methods claimed in instant claims 20-24 and 26. As such, a prima facie case of obviousness has not been established.

Applicants submit that the rejection of claims 20-24 and 26 under 35 U.S.C. § 103(a) has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Claim Rejections – Nonstatutory Double Patenting

Claims 20-22 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 18-19 of co-pending application U.S. Serial No. 10/303,160. It should be noted that the 10/303,160 application and Collins above are one and the same, and said application will be referred to hereinafter as "Collins".

With respect to claim 21, the Office asserts that while the exact wording of claim 1 of Collins is not the same as that of claim 21 of the instant application, the only difference in scope is in step (b) with the only difference being the additional requirement of the empirical evaluation employing a nucleic acid sample pair as

selected by claim 1 in the instant application versus just an empirical evaluation in clam 1 of the Collins application. The Office further asserts that the "empirical evaluation" step of claim 1 of Collins is generic to the "empirical evaluation employ[ing] a nucleic acid sample pair selected by a method according to claim 1" step of the instant claim 21. Finally, the Office points to paragraph 70, lines 6-10 of Collins and indicates that the disclosed species would anticipate the "empirical evaluation employ[ing] a nucleic acid sample pair" step of the instant claim.

Claim 1 of Collins is directed to a method of identifying a sequence of a nucleic acid that is suitable for use as a substrate surface immobilized probe for a target nucleic acid. The method comprises: (a) identifying a plurality of candidate probe sequences for the target nucleic acid based on at least one selection criterion; (b) empirically evaluating each of the candidate probe sequences under a plurality of different experimental sets to obtain a collection of empirical data values for each of the candidate nucleic acid probe sequences for each of the plurality of different experimental sets; (c) clustering the candidate probe sequences into one or more groups of candidate probe sequences based on each candidate probe sequence's collection of empirical data values, wherein each of the one or more groups exhibits substantially the same performance across the plurality of experimental sets; (d) selecting one of the one or more groups based on at least one criterion; and (e) choosing a candidate probe sequence from the selected group to as the sequence of the nucleic acid that is suitable for use as a substrate immobilized probe for the target nucleic acid. It is readily seen from claim 1 of Collins that what is disclosed is a method for identifying candidate probes for a target nucleic acid.

A double patenting rejection of the obviousness-type is "analogous to [a failure to meet] the nonobviousness requirement of 35 U.S.C. § 103 except that the patent principally underlying the double patenting rejection is not considered prior art. *In re Braithwaite*, 379 F.2d 594, 154 USPQ 29 (CCPA 1967). Therefore, any analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a 35 U.S.C. 103 obviousness determination. *In re Braat*, 937 F.2d 589, 19 USPQ2d 1289 (Fed. Cir. 1991); *In re Longi,* 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

Claim 1 of Collins does recite the following elements of claims 20-22, which

each depend respectively from claim 1 of the present application: (i) identifying a combination of nucleic acid sample pairs in relation to the members of said combination having a maximized number of genes from the set of genes that exhibit differential expression and a minimized number of genes from the set of genes that do not exhibit differential expression; and (ii) selecting said combination of nucleic acid sample pairs as the combination of nucleic acid sample pairs for evaluating the ability of an oligonucleotide probe to measure differential expression of genes.

At the top of page 14, the Office Action asserts that the portion of the Collins specification that supports the recited "empirical evaluation" procedure includes an embodiment that would anticipate the empirical evaluation employing a nucleic acid sample pair step of the instant claim 21. The Office contends that paragraph 70, lines 6-10, of Collins specifically discloses an empirical evaluation wherein the empirical evaluation employs a nucleic acid sample pair selected by a method of instant claim 1.

Applicants respectfully disagree. As discussed above with regard to the rejection of claim 1 over Collins, the above-cited passage from the reference discusses a representative example of the empirical evaluation step of the methods disclosed in Collins. Multiple copies of a microarray that includes candidate 60-mer probes having sequences identified by the prior sequence identification step were produced using an in situ nucleic acid array synthesis protocol. These resultant microarrays were then hybridized to 10 different tissue/cell line combinations (4 replicates per sample pair): one self-vs.-self and 9 sample pairs chosen to maximize the number of mRNA's that are differentially expressed between the members of the pair.

It is clear from the context of the above passage (see paragraphs 0048, *et seq.* of the reference) that Collins is discussing a method for identifying candidate probes for a target nucleic acid. At paragraph 48, Collins indicates that the invention provides methods of identifying a sequence of a nucleic acid that is suitable for use as a surface immobilized probe for a target nucleic acid. There is no disclosure or suggestion of (i) identifying a combination of nucleic acid sample pairs in relation to the members of said combination having a maximized number of genes from the set of genes that exhibit differential expression and a minimized number of genes from the set of genes that do not exhibit differential expression; and (ii)

selecting said combination of nucleic acid sample pairs as the combination of nucleic acid sample pairs for evaluating the ability of an oligonucleotide probe to measure differential expression of genes.

Claims 20 and 22 are not rendered obvious by claims 1 and 18-19 of Collins for reasons similar to those discussed above with regard to the rejection of claim 21.

Applicants submit that the provisional rejection of claims 20-22 under the judicially created doctrine of obviousness-type double patenting has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Claim Rejections - 35 U.S.C. § 102(f)

Claims 20-22 were rejected under 35 U.S.C. 102(f) because the applicant allegedly did not invent the claimed subject matter.

The Office apparently arrives at this rejection based on an interpretation of claims 1 and 18-19 of Collins as not patentably distinct from claims 20-22 of the instant application.

Applicants respectfully disagree with the above interpretation. As demonstrated above, the Collins does not disclose or suggest at least the following elements of claims 20-22, which each depend respectively from amended claim 1 of the present application: (i) identifying a combination of nucleic acid sample pairs in relation to the members of said combination having a maximized number of genes from the set of genes that exhibit differential expression and a minimized number of genes from the set of genes that do not exhibit differential expression; and (ii) selecting said combination of nucleic acid sample pairs as the set of nucleic acid sample pairs for evaluating the ability of an oligonucleotide probe to measure differential expression of genes.

Thus, Collin's claims are different from the instant claims in both emphasis and scope. As such, the Examiner has no reason to believe that the listed inventors did not invent the subject matter being claimed.

Applicants submit that the rejection of claims 20-22 under 35 U.S.C. 102(f) has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

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CONCLUSION

In view of the amendments and remarks above, Applicants respectfully submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone Bret E. Field, (650) 327-3400.

The Commissioner is hereby authorized to charge any additional fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-1078, order number 10030679-1.

Respectfully submitted,

Date: August 21, 2007

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